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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,593	11/14/2003	Hua Xu	056274-3451	3233

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,593	XU ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *17 and 24-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to the Amendment

The Amendment filed on 05/30/2006 in response to the previous Non-Final Office Action (11/30/2005) is acknowledged and has been entered.

Claims 1-30 are currently pending.

Claims 17 and 24-30 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-16 and 18-23 are currently under consideration.

New Rejections upon reconsideration:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 10-16, 18-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims encompass a genus of compounds defined solely by its principal biological property, i.e., GST-activated, which is simply a wish to know the identity of any material with that biological property. However, the written description in this case only sets forth a GST-activated anticancer compound having the formula shown in claim 3.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show

applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

The specification teaches (page 5, paragraph 0034) that a GST-activated anticancer compound is a compound comprising a glutathione or a glutathione analog chemically linked to a cytotoxic moiety which is released by cleavage from the glutathione or glutathione analog in the presence of one or more GST isoenzymes. Specifically, the specification teaches that suitable compounds include those disclosed in US Patent No. 5,556,942 (page 5, paragraph 0035). Thus, while the specification reasonably conveys GST-activated anticancer compounds disclosed in US Patent No. 5,556,942, the specification does not appear to be commensurate in scope with any and or all GST-activated anticancer compounds. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of compounds that encompass the genus of GST-activated anticancer compounds nor does it provide a description of structural features that are common to

the genus. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of GST-activated anticancer compounds, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the GST-activated anticancer compound of the formula shown in claim 3, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-16 and 18-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauvar et al. (US 5,955,432, 1999) (*referred to herein as Kauvar '432*) in view of Kauvar et al. (US 5,556,942, 1996, IDS) (referred to herein as Kauvar '942) as evidenced by USP Dictionary of USAN and International Drug Names (2005, of record).

Kauvar '432 teaches a method of protecting a subject from the destructive effects of a chemotherapeutic agent, including irradiation, comprising administering to a subject an effective dose of a glutathione analog (column 2, lines 48-55). With regards to the destructive effect, the patent teaches that the glutathione analogs mitigate the bone-marrow destructive effects of chemotherapeutic agents (abstract). With regards to the subjects, the patent teaches that the subjects include, but are not limited to, vertebrate subjects, particularly mammalian or human subjects (column 7, lines 20-23). With regards to the dose, the patent teaches that the dosage required depends of the nature of the subject, the nature of the condition, the manner of administration and the judgment of the attending physician, but will be in the range of 0.1-100 mg/kg per day for 10 to 40 days (column 7, lines 47-55). With regards to the administration of the glutathione analog, the patent teaches that the timing of administration of the glutathione analog with respect to the chemotherapeutic agent depends on the nature of the chemotherapeutic agent used (column 7, lines 56-59). For example, the patent teaches that when 5-FU is used for chemotherapy, administration seems advantageous about 24 hours subsequent to administration of the 5-FU, whereas administration of the glutathione analog about 24 hours prior to cisplatin treatment is effective (column 7, lines 60-65). Moreover, the patent teaches a method of treating tumors comprising administering a glutathione analog in combination with Melphalan, wherein the glutathione analog potentiated the inhibitory effect of Melphalan (column 10, *Example 2*).

Kauvar et al. do not explicitly teach that the glutathione analog is a GST-activated anticancer compound.

Kauvar '942 teaches (column 5, lines 36-41) a method of treating tumor cells comprising administering glutathione S-transferase-activated compounds (GST), wherein the glutathione-S transferase activated compound are selectively cleaved by the tumor cells to release a cytotoxic agent. With regards the GST-activated anticancer compounds, the patent provides (column 4, lines 22-26 and beginning with column 5, line 1 to column 8, line 53) compounds which appear to be 100% identical to the presently claimed GST-activated anticancer compounds, wherein the GST-activated compounds comprise a glutathione (GSH) coupled to a leaving group such as a phosphoramide mustard, phosphorodiamidate mustard, a chemotherapeutic agent, toxin, anti-inflammatory or steroid based drugs. In one embodiement, Kauvar '942 disclose a method of treating a tumor comprising administering 300 mg/kg of a GST activated anticancer compound referred to as TER 286 (column 20, lines 21-33). Moreover, the patent teaches (column 4, lines 37-40) that the GST-activated compounds of the invention are useful for the treatment of drug resistance in cancer cells. Furthermore, Kauvar '942 disclose (column 5, lines 42-49) that the GST-activated compounds provide a chemotherapeutic agent to a tumor cell while protecting the function of bone marrow. As such, the patent teaches that the glutathione S-tranferase-activated compounds are useful for selective treatment of target tissues, which contain compatible glutathione S-transferase isoenzyme, and simultaneously elevate the levels of GM progenitor cells in bone marrow (abstract). Although Kauvar '942 do not specifically teach that the GST-activated agent referred to as TER286 is the presently claimed canfosfamide, the claimed limitation would be an inherent property of the referenced compound because as evidenced by USP Dictionary of USAN and International Drug Names, canfosfamide hydrochloride is also referred to as TER 286 (page 155 to 156, last compound taught on page 155). Thus, the claimed compound appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the GST-activated compound does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252,

195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the glutathione derivative taught by Kauvar '432 with a GST-activated anticancer compound as taught by Kauvar '942. One would have been motivated to do so because each of the agents have been individually taught in the prior art as being effective at mitigating the bone-marrow destructive effects of chemotherapeutic agents. In addition, Kauvar '942 teach that on top of being a bone marrow protectant, the GST-activated anticancer compounds are also useful for selective treatment of target tissues, which contain compatible glutathione S-transferase isoenzyme. Thus, one of ordinary skill in the art would have reasonable expectation of success that by administering a GST-activated anti-cancer compound in combination with a chemotherapeutic agent, one would achieve a method of treating cancer, as well as, a method of mitigating the bone-marrow destructive effects of chemotherapeutics agents such as cisplatin.

Secondly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the chemotherapeutic agents taught by Kauvar '432 with a GST-activated anticancer compound as taught by Kauvar '942 because each of the agents have been individually taught in the prior art to be effective at treating cancer. The instant the instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, one of ordinary skill in the art would have reasonable expectation of success that by administering a GST-activated anti-cancer compound in combination with a chemotherapeutic agent, one would achieve a method of treating cancer, as well as, a method of mitigating the bone-marrow destructive effects of chemotherapeutics agents such as cisplatin.

Furthermore, it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to optimize the dosage and interval schedule of canfosfamide hydrochloride. One would have been motivated to do so because as taught by Kauvar '432, the dosages, formulations and administration schedules will vary in cancer patients compared to normal

patients. Therefore, where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. As such, one would have a reasonable expectation of success that by optimizing the administration schedule, one would achieve a successful method of treating cancer, as well as, a method of mitigating the bone-marrow destructive effects of chemotherapeutics agents such as cisplatin.

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Patent Examiner
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JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

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